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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,015	11/01/2001	Michael Gerard Kelly	AM100053	3339

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EXAMINER

HABTE, KAHSA Y

ART UNIT PAPER NUMBER

1624

DATE MAILED: 02/06/2003

6

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/003,015

Applicant(s)

KELLY ET AL.

Examiner

Kahsay Habte, Ph. D.

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-18 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)                      4) ☐ Interview Summary (PTO-413) Paper No(s) \_\_\_\_.
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)                      5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2-5.                      6) ☐ Other:

**DETAILED ACTION**

***Restriction/Election***

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:
  - I. Claims 1 (in part), 3-4 (in part), 7-12 (in part), and 18 (in part) drawn to compounds where **A** in formula I is C, CR<sub>10</sub>, or N and m=1 (5-membered ring)), classified in class 548, subclass various.
  - II. Claims 1 (in part), 3-4 (in part), 7-12 (in part), and 18 (in part) drawn to compounds where **A** in formula I is C, or CR<sub>10</sub> and m=2 (monoazine ring), classified in class 546, subclass various.
  - III. Claims 1 (in part), 3-4 (in part), 7-12 (in part), and 18 (in part) drawn to compounds where **A** in formula I is C, or CR<sub>10</sub> and m=3 (7-membered ring)), classified in class 540, subclass various.
  - IV. Claims 1 (in part), 2, 3-4 (in part), 5-6, 7-12 (in part), 13, 14-15 (in part), 16-17, and 18 (in part) drawn to compounds where **A** in formula I is N and m=2 (diazine ring), classified in class 544, subclass various.
  - V. Claims 1 (in part), 3-4 (in part), 7-12 (in part), and 18 (in part) drawn to compounds where **A** in formula I is N and m=3 (diazepine ring), classified in class 540, subclass various.

The inventions are distinct, each from the other because of the following reasons:  
Groups I-V are directed to structurally dissimilar compounds such that the variable core created by the varying definitions of **A** and **m** in formula I do not belong to the same

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recognized class of chemical compounds in the art, and references anticipating one invention, would not render obvious the others. For example 5-membered rings with one or two nitrogens are different from monoazines (one N in the six membered ring), are different from azepines (seven membered ring with one nitrogen), are different from diazine rings that are six membered rings with 2 nitrogens, are also different from diazepines that are seven membered ring with 2 nitrogens. Thus, separate searches in the literature as well as in the U.S. Patent Classification System would be required. Each group's compounds are made and used independently of each other and could support separate patents. The compounds differ significantly in chemical structures. One skilled in the art would not consider such diverse structure equivalents of each other.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions anticipated by prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Because these inventions are distinct for the reasons given above and have acquired separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Ms. Barbara Lences on April 15, 2002 a provisional election was made with traverse to prosecute the invention of Group IV,

claims 1 (in part), 2, 3-4 (in part), 5-6, 7-12 (in part), 13, 14-15 (in part), 16-17, and 18 (in part). Affirmation of this election must be made by applicant in replying to this Office action.

### ***Abstract***

2. The abstract is defective for the following reasons:
  - a. The definition of variables A, X, Y, and m are missing.
  - b. The title of the invention (first two lines of the abstract) should be deleted from the abstract.

### ***Objection***

3. Claims 1, 3-4, 7-12, and 18 are drawn to multiple inventions for reasons set forth in the above requirement for restriction. The claims are examined only to the extent that they read on the elected invention. Applicants have to limit their invention to Group IV (piperazines, A=N and m=2).

### ***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-8 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There has been recited a method for the treatment of a disorder of the central nervous system (CNS) related to or affected by the 5-HT6 receptors in a patient, but the specification is not enabled for said disorder.

A number of factors are relevant to whether undue experimentation would be required to practice the claimed invention, including "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

(1). Breadth of Claims: Claim 7 is directed to a method of treatment for the disorder of the central nervous system related to or affected by the 5-HT6 receptors in a patient.

a. Scope of use - The scope of use that applicants intend to claim may well be very broad. Applicants intend to claim compounds that bind to 5-HT6 receptors. On page 3 (line 30-31) of the specification, it has been disclosed that there are no known fully selective agonists. Even if applicants' compounds are 5-HT6 receptor antagonists for treating of central nervous system related disorders, applicants did not show that

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central nervous system disorders that are related or affected by the 5-HT<sub>6</sub> receptors could be treated. Note that there is no mention of the treatment of CNS in the reference by Russell MG and Dias R. (Curr. Top. Med. Chem, 2002 June; 2(6):643-54). The reference only mentions the possible role of 5-HT<sub>6</sub> receptor antagonists in the treatment of learning and memory disorders, which is very narrow in scope.

With regard to claim 8, there have been recited the treatments of motor disorder and cognitive disorder, but motor disorder and cognitive disorders are very broad in nature. Motor disorders differ one from the other, the same is true for cognitive disorders. Please see below for details.

**Motor disorders** comprise a large component of impairment of neurological afflictions. They are contributed by a wide spectrum of disorders including Cerebral Palsy, Traumatic Brain Injury, Strokes, Demyelinating disorders (such as Multiple Sclerosis) and Hypoxic-Ischemic Injuries (i.e. damage from oxygen or blood flow deprivation, such as in near drowning injuries). In the newborn period, Brachial Plexopathies (e.g. Erb's Palsy), Spinal Cord Injuries, and Congenital Torticollis (Wry Neck) add to the number of pediatric motor disabilities.

Non traumatic and/or genetic pediatric movement disorders comprise the bulk of functional motor disabilities. These include Motor Tic Disorders, Tourette's Syndrome and the Dystonias. Motor disabilities are the dominant feature of the disability in these diagnoses and are the leading cause of their morbidity and economic impact. Motor

disorders lead to a veritable cascade of medical and social consequences with direct impact on quality of life, on health care costs and societal cost: pain, suffering, physical impairment, and tremendous expense are associated with motor disabilities. Surgeries, physical and occupational therapy for joint contractures (joint and muscle stiffening), the need for increased levels of daily care and assistance need to be included in the impact of many of these brain and spinal cord disorders.

Cerebral Palsy is a disorder resulting in a non-progressive, but often changing, disorder of movement and posture. The disorder arises from lesions or anomalies of the brain occurring during fetal development or the prenatal period. A health care system with a neonatal intensive care nursery therefore has a significantly higher exposure to this syndrome. The incidence of cerebral palsy is not declining despite changes in obstetrical care. Spasticity, incoordination, and ataxia are the most common motor disabilities following head injury. Movement disorders require a multidisciplinary team approach given the complexity of diagnosis and treatments involved.

**Cognitive Disorders** – are disorders in a brain that prevents someone from thinking well, from solving problems, or from storing information. Three main types of cognitive disorders are: Delirium, Dementia, and Amnesia.

Delirium - is a severe disturbance in consciousness and thought that is not better accounted for by dementia. Delirium is likely to have a sudden onset, be variable, and have a better chance of remission than dementia. Delirium involves disorientation and

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memory loss, along with distorted consciousness and cognitive deficits. The victim may not know what time it is, or where she or he is, or be able to speak coherently. Short-term memory loss is almost always noted. The patient is usually agitated, with the agitation worse at night; if in the hospital, the patient may fight, break things or tear out intravenous tubes, and have to be restrained. The onset of delirium is typically fairly sudden, taking a few hours to a few days, and delirium rarely lasts for more than a month; unfortunately, one reason for this is that the patient may die. Especially for this reason, the occurrence of delirium is a clear medical emergency calling for prompt treatment. One cause of delirium is substance intoxication via overdoses of drugs or exposure to toxins, or withdrawal from drugs. Another is various medical conditions, brain trauma caused by an accident or stroke, for example. The type of delirium is determined by what caused it; for example, two types are substance intoxication delirium and delirium caused by a medical condition.

If intoxication or treatable medical problems are detected and treated, the delirium is probably reversible. If treatment is not possible, permanent brain damage is either present or likely to develop, and the delirium may progress to dementia.

Delirium can be subcategorized into one of the following depending on the causes:

- From substance intoxication

- From withdrawal

- From multiple causes

Other cognitive disorders include autism, ADHD, schizophrenia, and other forms of psychosis.

Dementia, like delirium, involves cognitive deficits, but the deficits are different. One universal characteristic of dementia is short-term memory loss. It may be accompanied by inability to find words (aphasia), to recognize objects (agnosia), or to carry out a sequence of motor activities (apraxia), despite the ability to make the individual movements. The onset of dementia tends to be more gradual than the onset of delirium, and may go unnoticed for long periods. The person with dementia may behave quite inappropriately, for example by telling dirty jokes to strangers or exposing genitalia. Violent behavior, although less common than in cases of delirium, sometimes occurs. In early cases of dementia, when the individual is aware of his or her deteriorating condition but still able to execute plans, suicide is a possibility.

Just as in delirium and many other disorders, the subtypes of dementia are classified according to their causes. An increasingly common type of dementia is dementia of the Alzheimer's type; estimates place the percentage of people over 65 in the United States with Alzheimer's at 2 to 4 percent.

Despite the fact that many causes of dementia are age-related, one should not assume that dementia is a normal consequence of aging. Although little can be done to prevent or ameliorate dementia in many cases, a medical examination is necessary in order to evaluate causes and possible treatments. One study of cases of dementia at three centers showed that 26% of the cases were treatable. The most common treatable

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cases are those with chronic drug toxicity, major depression, normal pressure hydrocephalus, or operable brain masses.

Future research may uncover, one type at a time, ways to prevent or treat the dementias; some drugs already show promise in arresting the progress of Alzheimer's disease. Other types of dementia include: Alzheimer's Disease, Creutzfeldt-Jacob Disease, HIV Dementia, Pick's Disease, Vascular Dementia, Substance-Induced Persisting Dementia, Dementias that can arise from head trauma, Huntington's Disease, Parkinson's disease.

Amnesia - is loss of memory; it is retrograde if memories before a fixed event are lost, and anterograde if memories after a fixed event are lost. An individual may have both kinds of amnesia.

Amnesias, as the name indicates, are characterized by memory losses without sufficient cognitive deficits to indicate a diagnosis of delirium or dementia, and can be subcategorized into those: Caused by medical conditions, Caused by substance abuse, etc.

As shown above, the disorders of central nervous system (CNS) are very broad and the disorders also vary one from the other. It is also shown that cognitive and motor disorders are also broad in nature and the disorders vary one from the other. The burden is on applicants, to show that their compounds can treat the disorders that are listed above.

b. Scope of Compounds - The scope of the compounds is also broad. It is apparent that hundreds of millions of combinations of compounds can be created from the definitions, owing especially to broad scope of R1-R8.

(2). Direction of Guidance: Applicants indicate that compounds that are capable of forming 5-HT6 receptor ligands are potentially useful in the treatment of a number of central nervous system disorders (page 1). The amount of direction or guidance is minimal. There is no guidance for the treatment of CNS disorders that are related or affected by 5-HT6 receptors. What diseases are those? Dosage is generic to the disorders - same dosage for all disorders. The specification fails to teach whether the compounds act as agonists, antagonists, partial agonists, reverse agonists, etc.

(3). State of Prior Art: There is no evidence of record that compounds structurally similar to these 1-aryl or 1-alkylsulfonyl heterocyclobenzazoles as 5-HT6 ligands or indeed are in use for the treatment of CNS disorders, let alone CNS in general. Applicants' compounds contain fully or partially saturated pyrimidine that is directly attached to benzo-fused five membered ring with 1-2 heteroatoms, which is structurally different than the compounds 9 and 10 on page 646 of the article.

(4). Working Examples: The affinity of test compounds for the binding of 5-HT6 receptor was performed on 53 compounds. Four out of 103 compounds failed to bind to 5-HT6 receptor. Some of the compounds show such poor binding towards 5-HT6

receptor that one would consider it to be of no value. There is no way to convert this data into specific useful knowledge, especially in view of the difficult nature of some of these disorders.

(5). Nature of the Invention and Predictability: The invention is directed to treating CNS disorders that are related or affected by 5-HT<sub>6</sub> receptors. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). CNS disorders are especially unpredictable due to their complex nature. Please refer below in item 5 to see how broad neurodegenerative disorders (part of CNS disorders) are. The treatment of one type of CNS disorder could not be necessarily the same for the other type.

(6). The Relative Skill of Those in the Art: The relative skill is extremely very low. To this day, there is no magic bullet that can treat CNS disorders. Many cognitive disorders have no treatment at all, e.g. autism, amnesia from alcohol blackouts.

According to a review article by Russell MG and Dias R. (Curr. Top. Med. Chem, 2002 June; 2(6):643-54), "the study for the possible role of 5-HT<sub>6</sub> receptor antagonists in the treatment of learning and memory disorders has stimulated significant recent work in this area", indicating that the study is at its early stage. According to the article

(page 652, first paragraph), it has been concluded: "these data are open to very different interpretations which directly oppose the proposed role for 5-HT6 receptor antagonists as potential enhancers." The above statement surely contradicts the use of applicants' compounds for the treatment of cognitive disorders as recited in claim 8. This fundamental, unresolved contradiction shows how low is skill level in this art. According to said article (page 650, last paragraph), it has been cited that "the current lack of full data supporting a role for 5-HT6 receptor antagonists in either behavioral inflexibility or in cognition enhancement *per se*, ... Certainly, the findings from both water maze studies are interesting and follow-up studies would be recommended." The article clearly shows that supporting data is needed for the role of 5-HT6 receptors as antagonists in behavioral inflexibility or in cognition enhancement, and that basic understanding is still lacking.

According to the article (see 648, second column last paragraph): "there are a number of potential problems regarding the behavioral findings described above. One concern is the relatively poor brain penetration ..." The cited reference in the conclusion (page 652) points out that additional studies are required to both replicate and further investigate the functional role of the 5-HT6 receptor. In fact the authors concluded: "Indeed, to date, findings from *in vivo* studies which have attempted to shed light on 5-HT6 receptor function are ambiguous and somewhat controversial." It is clear from the article that the study is at its early stage as of June 2002 (after the filing date of the instant case). It certainly requires undue experimentation to determine which central nervous system disorders are related or affected by the 5-HT6 receptors given how little

is actually known about the function of 5-HT6 receptor. Despite the discrepancies noted on the article in regard to the research, applicants intend to claim the treatment of any CNS disorders that are related or affected by 5-HT6 receptors. It is up to applicants to show a publication that shows that their compounds can act as agonists or antagonists to treat CNS diseases that are related or affected by 5-HT6 receptors.

- (7). The Quantity of Experimentation Necessary: Immense, because of points (1), (2) and (6).

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

5. Claims 10-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In claim 10, there has been recited a method of treating neurodegenerative disorder but the specification is not enabled for the treatment of neurodegenerative disorder.

A number of factors are relevant to whether undue experimentation would be required to practice the claimed invention, including "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

(1). Breadth of Claims: Claims 10-11 directed to a method of treatment for neurodegenerative disorder.

a. Scope of use - The scope of use that applicants intend to claim (neurodegenerative disorders) is very broad.

It has been recited in claim 10, a method of treating neurodegenerative disorders. There is no such an agent, which can treat neurodegenerative disorders generally. The term "neurodegenerative disorders" covers a broad array of different disorders that have different modes of action and different origins. The term covers such diverse disorders as Alzheimer's Disease; Parkinson's Disease; ALS and variants such as forms of ALS-PDC; dementia of the frontal lobe type (DFT) and DFT with motor neuron disease (DFT-MND); Diffuse Lewy Body Disease; Hallervorden-Spatz disease; progressive familial myoclonic epilepsy; Corticodentatonigral degeneration; more than a dozen dementias

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collectively called "frontotemporal dementia" (FTD); Tourette's syndrome; Shy-Drager syndrome;; Friedrich's ataxia and other spinocerebellar degenerations; Olivopontocerebellar atrophy (OPCA); spasmodic torticollis; Striatonigral degeneration; various types of torsion dystonia; certain spinal muscular atrophies, such as Werdnig-Hoffmann and Wohlfart-Kugelberg-Welander; Hereditary spastic paraplegia, Primary lateral sclerosis; peroneal muscular atrophy (Charcot-Marie-Tooth); Hypertrophic interstitial polyneuropathy (Dejerine-Sottas); ophthalmic disorders such as primary open-angle glaucoma (POAG) and retinitis pigmentosa; Leber's Disease; Wallerian degeneration, assorted prion diseases, and Hypertrophic interstitial polyneuropathy. There is a group of Prion diseases, notably Creutzfeldt-Jakob Disease (CJD), which occurs in both sporadic and familial forms; Gerstmann-Straussler-Scheinker Disease (GSS); and fatal familial insomnia. There is another group called the Taupathy diseases, which include Pick's disease; cortical-basal ganglionic degeneration (CBGD or CBD); progressive supranuclear palsy (PSP); and the amyotrophic lateral sclerosis/Parkinsonism-dementia complex. Another group is the Polyglutamine diseases: Huntington's disease; spinal-bulbar muscular atrophy (Kennedy's disease or SBMA), Dentatorubral-Pallidoluysian Atrophy (DRPLA), Machado-Joseph disease (MJD, also called spinocerebellar ataxia type 3), and the other SCA diseases, viz SCA-1, SCA-2, SCA-6, and SCA-7.

These exhibit a very broad range of effects and origins. For example, some give no dementia and affect only vision, such as POAG. Some give progressive dementia without other prominent neurological signs, such as Alzheimer's disease, whereas other

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dementias do have such signs, such as Diffuse Lewy Body Disease. Many give distinctive and different patterns of effect. For example, FTDs, which have bilateral atrophy of the frontal and anterior temporal lobes, produce progressive nonfluent aphasia and semantic dementia, but, in contrast to e.g. Alzheimer's disease, visuospatial skills and day-to-day memorizing is largely unaffected. Some give muscular wasting without sensory changes, e.g. ALS, and some do have the sensory changes such as Werdnig-Hoffmann. Some affect only vision such as retinitis pigmentosa, while others affect both vision and cognitive functions, such as Posterior cortical atrophy (PCA). Some are abnormalities of posture, movement or speech, such as Striatonigral degeneration, and other are progressive ataxias, such as OPCA. Some give an extremely broad range of effects. For example, CBD can give apraxia, alien limb phenomenon, cortical sensory loss, aphasia, myoclonus, bradykinesia, rigidity, dystonia, tremor, memory impairment and/or personality/behavioral changes.

The toxic protein involved also varies. In some cases it is tau, especially Alzheimer's disease and Taupathy, and some are so linked to tau only sometimes (FTD). Alzheimer's Disease also involves beta-amyloid. For Parkinson's disease it is  $\alpha$ -synuclein, while ALS is linked to SOD1. Prion disease involves PrP<sup>Sc</sup> as its toxic protein, which involves missense. The polyglutamine diseases involve polyglutamine-containing proteins. For Huntington's disease, it is huntingtin, for SBMA it is an androgen receptor, for DRPLA it is atrophin, for SCA-1 it is Ataxin-1, for SCA-2 it is Ataxin-2, for SCA-3 it is Ataxin-3, for SCA-6 it is calcium channel protein, and for SCA-7 it is Ataxin-7.

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The nature of the protein deposits varies as well. In Alzheimer's disease, there are extracellular plaques from beta-amyloid and neurofibrillary tangles (from tau). In Parkinson's disease it is Lewy bodies and in ALS it is Bunina bodies. Taupathy produces cytoplasmic tangles, and Polyglutamine disease produce neuropil aggregates, intranuclear inclusions and cytoplasmic tangles. Prion disease produces prion plaque.

And note that the disease form is not necessarily related to the protein deposits. For example, Alzheimer's disease and Pick's disease both give progressive dementia without other prominent neurological signs. But the characteristic Alzheimer's neurofibrillary tangles are not seen in Pick's Disease, which has straight fibrils, as opposed to the paired helical filaments of Alzheimer's disease. Pick's Disease gives lobal atrophy, not seen in Alzheimer's disease.

The disease genes vary considerably as well. In Alzheimer's disease, there is toxic gain of function with APP and loss of function of Presenilin 1 and presenilin 2. With Parkinson's disease, there is toxic gain of function with -synuclein, and loss of function of Parkin and UCHL1. In the Polyglutamine diseases, there is toxic gain of function with 9 different genes with CAG repeat expansion. In Prion disease, there is toxic gain of function with PRNP. In ALS there is toxic gain of function with SOD1. FTDP-17 arises from mutations at chromosome 17, Huntington's disease from chromosome 4, and the neurodegenerative disorder that people with Down's syndrome develop later in life is presumably connected in some way to chromosome 21.

There are differences in origins, even with what little is known. Thus, among progressive dementias, CJD is definitely caused by an infectious agent; so far as can be

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determined, this is not so for Huntington's disease. Even among the hereditary disorders, the origins are clearly different.

In regard to the method of treatment for Alzheimer's disease and Parkinson's disease, applicants are directed to see part (a) for details.

b. Scope of Compounds - The scope of the compounds is also broad. It is apparent that hundreds of millions of combinations of compounds can be created from the definitions, owing especially to broad scope of R1-R8.

(2). Direction of Guidance: Applicants indicate that compounds that are capable of forming 5-HT6 receptor ligands are potentially useful in the treatment of a number of central nervous system disorders (page 1). The amount of direction or guidance is minimal. There is no guidance for the treatment of neurodegenerative disorders especially for Alzheimer and Parkinson's disease. Dosage is generic to the disorders - same dosage for all disorders. The specification fails to teach whether the compounds act as agonists, antagonists, partial agonists, reverse agonists, etc.

(3). State of Prior Art: There is no evidence of record that compounds structurally similar to these 1-aryl or 1-alkylsulfonyl heterocyclobenzazoles as 5-HT6 ligands or indeed are in use for the treatment of neurodegenerative disorders, let alone

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Alzheimer's disease and Parkinson's disease that are hard to treat. Applicants' compounds contain fully or partially saturated pyrimidine that is directly attached to benzo-fused five membered ring with 1-2 heteroatoms, which is structurally different than the compounds 9 and 10 on page 646 of the article.

(4). Working Examples: The affinity of test compounds for the binding of 5-HT6 receptor was performed on 53 compounds. Four out of 103 compounds failed to bind to 5-HT6 receptor. Some of the compounds show poor binding towards 5-HT6 receptor. There is no way to convert this data into specific useful knowledge.

(5). Nature of the Invention and Predictability: The invention is directed to treating CNS disorders that are related or affected by 5-HT6 receptors. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Neurodegenerative disorders are especially unpredictable due to their complex nature.

(6). The Relative Skill of Those in the Art: The relative skill is extremely very low. To this day, there is no magic bullet that can treat neurodegenerative disorders in general.

According to a review article by Russell MG and Dias R. (*Curr. Top. Med. Chem*, 2002 June; 2(6):643-54), "the study for the possible role of 5-HT(6) receptor antagonists in the treatment of learning and memory disorders has stimulated significant recent work in this area", indicating that the study is at its early stage. According to the article (page 652, first paragraph), it has been concluded: "these data are open to very different interpretations which directly oppose the proposed role for 5-HT6 receptor antagonists as potential enhancers." The above statement surely contradicts the use of applicants' compounds for the treatment of neurodegenerative disorders as recited in claims 10-11. This fundamental, unresolved contradiction shows how low is skill level in this art. Said reference by Russell et al., which is a very recent review article, does not mention any treatment for neurodegenerative disorders, Alzheimer's disease or Parkinson's disease.

The great majority of the neurodegenerative disorders have no treatment at all, and of those that do, none or virtually none have been treated with such inhibitors as are disclosed here. The great diversity of diseases falling within the "neurodegenerative disorder" category means that it is contrary to medical understanding that any agent (let alone a genus of trillions of compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. Further, what little success there has been does not point in this direction. Thus, what very few treatments that the massive

research effort on Alzheimer's disease has produced are means of providing Acetylcholinesterase inhibition, unrelated to the mechanism of action in this case.

The central characteristic of Alzheimer's disease is the deficiency in the level of the neurotransmitter Acetylcholine that plays an important role in memory. Alzheimer's disease can be treated only by Acetylcholinesterase inhibitors that reduce the depletion of acetylcholine. The skill level in the art is so low that the only treatments available to this day are drugs that inhibit Acetylcholinesterase. It is up to applicants to show that their compounds can reduce the depletion of acetylcholine.

Parkinson's disease is a neurological disorder that is also characterized by rhythmic muscle tremors, hypokinesia, and muscular rigidity. Dopamine, a hormonelike substance is an important neurotransmitter in both the central and peripheral nervous systems that is currently used as treatment for Parkinsonism. Dopamine is a neurotransmitter involved in the regulation of the central nervous system. The skill level in the art is such low that the only treatments available to this day are drugs that are helpful in regulating Dopamine. Thus, a rejection under 35 U.S.C. 112, first paragraph is proper. It is up to applicants to show that their compounds can regulate Dopamine.

Russell et al. conclude: "Indeed, to date, findings from *in vivo* studies which have attempted to shed light on 5-HT<sub>6</sub> receptor function are ambiguous and somewhat controversial." It is clear from the article that the study is at its early stage as of June

2002 (after the filing date of the instant case). It certainly requires undue experimentation to determine which neurodegenerative disorders are related or affected by the 5-HT6 receptors given how little is actually known about the function of 5-HT6 receptor. Despite the discrepancies noted on the article in regard to the research, applicants intend to claim the treatment of any neurodegenerative disorders, especially AD and Parkinson's disease. It is up to applicants to prove that their compounds can act as agonists or antagonists to treat neurodegenerative disorders, Alzheimer's disease, or Parkinson's disease.

- (7). The Quantity of Experimentation Necessary: Immense, because of points (1), (2) and (6).

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

### ***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

✓ a. In claim 1 or elsewhere in the claims, the phrase "optionally substituted" is indefinite. Substituted by what? What are included and what are not? Applicants have to recite the substituents in the claims, assuming there is enough support in the specification.

? b. In claims 1, 5, 7 or elsewhere in the claims, the term "cycloheteroalkyl" is not clear. What is it? Is it cycloalkyl or carbocycle attached to a heteroalkyl (e.g. cyclohexyl-NH-alkyl)? Is it a heterocycle (e.g. pyridine)? This is not a standard chemical name.

✓ c. In claim 7, there has been recited a method for the treatment of a disorder of the central nervous system related to or affected by the 5-HT<sub>6</sub> receptor. The scope of claim 7 is unknown. Which diseases are these? Determining whether a given disease responds or does not respond to bind to such receptor will surely involve undue experimentation. Suppose that a given ligand X when administered to a patient with Disease D does not obtain a response. Does one then conclude that Disease D does not fall within this claim? Keep in mind that:

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A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?

B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another which is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? Thus, how many dosages and dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?

C. It may be that X simply isn't potent enough for Disease D, but that another inhibitor Y is potent enough, so that D really does fall within the claim. Thus, how many different mediators must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property which Y is capable of. Thus, when mixed results are obtained, how many more pharmaceuticals need be tested?

E. Finally, suppose that X really will work, but only when combined with Z. There are for example, agents in the antiviral and anticancer technology which are not themselves effective, but the disease will respond when the agents are combined with something else.

F. In addition, literally speaking, any disorder can be treated with any drug, although the treatment might not be successful. Assuming that "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000?

As a result, determining the true scope of the claim will involve extensive and potentially open-ended research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Note that it is also unclear which disorders from either cognition disorder or motor disorder are covered. There is no guidance in the specification or from the reference (Russell MG and Dias R. *Curr. Top. Med. Chem*, 2002 June; 2(6):643-54).

### **Conclusion**

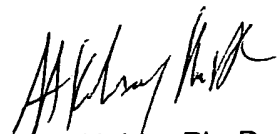
8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (703) 308-4717. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 703-308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.



Kahsay Habte, Ph. D.  
Examiner  
Art Unit 1624

KH  
February 4, 2003



Mark L. Berch  
Primary Examiner  
Art Unit 1624